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Various Bioactivity and Relationship of Structure−Activity of Matrine Analogues

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Supporting Information

ABSTRACT: For the first time, the botanic source natural product matrine was reported to have more potent inhibitory activity against tobacco mosaic virus (TMV) than the commercial virucide ribavirin. On the basis of the structural diversity modification strategy, a series of matrine derivatives was synthesized and systematically evaluated for their antiviral activity against TMV, fungicidal activity, and insecticidal activity. As a result, compounds **3** (inhibitory rate 67.3%, 69.5%, 63.7%, 63.0% at 500 μg/mL for in vitro activity, inactivation, curative, and protection activities in vivo, respectively), **16** (66.7%, 60.7%, 63.8%, 68.9% at 500 μg/mL), and **32** (74.6%, 76.9%, 72.3%, 75.7% at 500 μg/mL) were found to have much higher anti-TMV activity than ribavirin (40.8%, 37.5%, 38.2%, 37.7% at 500 μg/mL), even exhibiting as well as NK-007 (70.3%, 66.1%, 68.4%, 67.5% at 500 μg/mL), which was an efficient compound created by our group previously. At the same time, it was found that matrine and its derivatives had a broad spectrum fungicidal activity (14 fungi), especially the inhibition of compound **32** against *Phytophthora capsici Leonian* reached 96.4% at a concentration of 50 μg/mL. What's more, all compounds exhibited very good insecticidal activity to five kinds of insects (including *Mythimna Separate*, *Helicoverpa Armigera*, *Ostrinia Nubilalis*, *Plutella xylostella*, and *Culex Pipiens Pallens*); especially, the inhibition rate of *C. Pipiens Pallens* of compound **22** could still reach 70% at 1 μg/mL.

KEYWORDS: *natural product of plant sources, matrine, anti-TMV activity, fungicidal activity, insecticidal activity, structure−activity relationship*

INTRODUCTION

Matrine alkaloids, including matrine, oxymatrine, sophocarpine, and oxysophocarpine,[1,2] etc. (Figure 1), are the main effective components of Chinese herbal medicine such as *Sophora flavescens*, *Sophora alopecuroides*, and *Sophora subprostrara*.[3] Matrine was isolated from the root of Kushen in 1889 first by Japanese scholars, and its structure was confirmed by Kondo in 1936.[4]

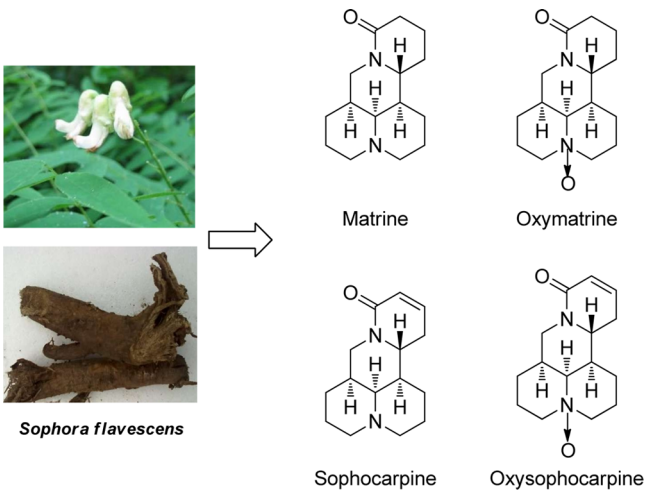

Figure 1. Matrine alkaloids.

Matrine and total matrines (total alkaloids extracted from certain Sophora species) were reported to have various medicinal activities, such as antipyretic,[5] analgesic,[6] and anti-inflammatory activities,[7] and they were used for treatment of lipopolysaccharide-induced liver injury.[8] As a botanical pesticide and being friendly to natural environment, the total matrines have also been commercialized as a broad spectrum insecticide (that was named by Kudun); however, their insecticidal activities were two orders of magnitude lower than the world's most popular pesticides discovered by the international pesticide companies in the last ten years.

Recently, the synthesis and bioactivity study on matrine analogues had been investigated extensively in China. However, most researches mainly focused on the antitumor activity,[9−15] antiangiogenesis,[16] antioxidant activity,[17] and antiviral activity;[18−20] comparably, the study on the agricultural use such as antiplant virus activity, fungicidal activity, and insecticidal activity[21] was not as much.

As one of our everlasting projects on the application of natural products, the botanical source product matrine was evaluated its inhibitory activity against tobacco mosaic virus (TMV) for the first time, and matrine was found to exhibit higher anti-TMV

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Table 1. In Vitro and in Vivo Antiviral Activities of Ribavirin, NK-007, Matrine Analogues, and Compounds 1−30 against TMV[a]

compd	conc (μg/mL)	in vitro inhibition rate (%)	in vivo inactivation effect (%)	in vivo curative effect (%)	in vivo protection effect (%)
ribavirin	500	40.7±0.7	38.5±0.9	36±0.5	39.8±0.4
	100	9.6±0.3	8.4±0.3	13.9±0.5	11.3±0.1
NK-007	500	65.4±0.6	67.8±1.0	66.9±0.6	70.2±0.7
	100	21.9±0.3	25.8±0.7	23.7±0.3	28±0.2
matrine	500	44.7±0.9	45.7±1.0	42.8±1.3	44.4±0.9
	100	21.5±0.5	18.9±0.6	15.6±0.5	20.5±0.4
1	500	52.3±1.0	49.2±2.0	50±0.8	48.7±0.7
	100	27.2±0.6	22.5±1.6	30±0.4	28±0.5
2	500	37.3±1.7	40±1.9	43.5±0.7	36.4±0.6
	100	12±0.5	15.9±1.5	18.4±0.6	7.7±0.4
3	500	67.3±0.8	69.5±1.8	63.7±1.9	63.0±0.7
	100	23.4±0.5	32.0±1.0	25.1±0.3	30.9±0.5
4	500	43.5±0.7	41.2±1.7	35.9±0.6	37.3±0.5
	100	0	10.9±0.7	12.4±0.5	18.0±0.5
5	500	35.8±0.8	45.2±1.3	39.7±0.8	49.8±0.7
	100	20.9±0.6	12.1±1.5	18.8±0.3	15.3±0.3
6	500	59.4±0.9	57.8±2.3	52.4±1.1	55.9±0.9
	100	27.5±1.0	22.9±0.8	19.8±1.5	21.2±1.0
7	500	47.1±0.8	55.6±3.0	52.4±1.0	58.9±0.8
	100	18.6±0.5	19.2±1.5	23.5±0.5	26.3±0.3
8	500	50.0±1.0	53.8±1.0	56.9±0.8	51.7±1.3
	100	20.2±0.6	15.3±1.1	12.8±0.4	23.2±0.8
9	500	48.3±1.1	50.3±2.1	41.2±1.2	47.5±0.9
	100	11.9±0.7	22.2±1.0	13.1±0.5	23.6±1.0
10	500	43.3±1.0	45.5±2.5	50.4±0.9	42.1±1.0
	100	8.6±0.3	16.8±0.4	24.3±0.3	18.9±0.4
11	500	41.6±0.9	49.8±1.7	46.2±0.8	50.7±1.0
	100	18.0±1.0	21.0±1.3	16.9±0.6	24.4±0.9
12	500	54.0±1.2	56.2±2.5	45.8±1.1	44.2±1.3
	100	18.9±0.7	20.0±1.2	23.7±0.6	16.5±1.0
13	500	46.9±0.6	44.5±1.1	40.8±0.8	41.7±0.6
	100	9.7±0.7	20.5±1.0	11.4±0.7	14.0±0.4
14	500	54.0±1.0	63.5±1.7	62.4±1.5	58.3±1.0
	100	25.8±1.1	28.9±1.1	21.0±0.8	25.0±0.6
15	500	46.8±0.5	43.5±1.0	37.2±1.0	45.1±1.0
	100	11.2±0.3	17.5±0.7	0	16.4±1.0
16	500	66.7±1.5	60.7±2.0	63.8±1.1	68.9±1.0
	100	34.1±0.7	26.3±1.0	29.0±0.9	32.2±0.6
17	500	42.3±1.3	36.8±2.4	36.1±0.9	31.5±0.6
	100	18.4±0.2	4.6±1.4	5.9±0.3	0
18	500	52.3±2.0	49.1±3.6	46.5±3.3	41.7±0.6
	100	18.4±1.1	4.6±0.7	5.9±2.6	0
19	500	38.3±1.0	46.8±1.4	41.9±1.2	44.7±1.1
	100	0	0	12.4±2.1	18.5±1.0
20	500	43.5±0.8	45.2±2.2	48.7±1.0	53.8±0.9
	100	0	19.2±1.0	16.6±0.8	23.3±0.6
21	500	50.7±1.3	49.4±0.9	53.7±2.4	50.8±1.7
	100	19.2±1.0	19.3±3.1	23.8±0.1	10.5±0.6
22	500	46.4±1.8	42.5±1.1	54±0.8	52.6±2.0
	100	10.9±2.0	29.1±0.7	19.2±0.5	14.0±0.2
23	500	54.9±2.0	61.8±3.7	65.8±0.5	56.9±1.0
	100	23±1.1	31.1±1.0	28.2±3.4	26.4±2.2
24	500	49.8±2.2	47.7±1.9	44.0±0.7	51.2±2.0
	100	11.5±1.0	16.3±0.8	21.1±2.8	14.9±0.9
25	500	31.9±1.5	45.2±2.0	40.3±0.8	46.7±4.2
	100	0	8.3±1.4	13.6±0.6	11.0±0.3
26	500	52.3±2.0	49.1±3.7	46.5±3.7	41.7±3.7
	100	18.4±0.7	4.6±0.6	5.9±0.4	0
27	500	46.2±1.3	49.0±1.9	42.3±1.0	54.0±1.0
	100	8.1±1.2	13.5±1.0	16.7±0.6	10.2±1.0
28	500	36.0±0.9	51.3±3.0	43.1±1.5	48.9±0.9
	100	19.3±1.0	23.8±0.8	15.2±0.6	7.1±1.3
29	500	58.6±1.3	47.9±1.6	52.6±0.7	56.0±1.2
	100	24.0±1.0	19.8±1.3	22.3±0.3	24.5±0.7
30	500	53.2±2.1	52.0±2.8	60.7±1.0	58.8±1.0
	100	27.6±0.8	14.3±0.6	22.4±0.6	30.4±1.0

[a]The data are presented in means ± SD.

activity than commercialized ribavirin in four modes (in vitro, inactivation effect, curative effect, and protection effect in vivo) (Table 1). Thus, in this report, a series of matrine derivatives (Figure 2), especially the esters of 14-hydroxymethyl-15-deoxymatrine, was synthesized to seek more potent anti-TMV compounds. Fungicidal and insecticidal activities of matrine and its derivatives were also evaluated systematically.

MATERIALS AND METHODS

Instruments and Chemicals. Matrine was from Baoji Biological Development Co. Ltd. Reagents were purchased from commercial sources and were used as received. All anhydrous solvents were dried and purified by standard techniques just before use. Reaction progress was monitored by thin-layer chromatography on silica gel GF254 with detection by UV. Melting points were determined using an X-4 binocular microscope melting point apparatus, and the thermometer was uncorrected. ^{1}H NMR spectra were obtained by using Bruker AV 400 with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using a Bruker AV 400 (100 MHz) with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) were reported in parts per million using the solvent peak as standard. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T).

The synthetic routes are given in Figure 3.

*Synthetic Procedure for 15-Deoxymatrine (**1**).* To a suspension of $LiAlH_4$ (0.46 mg, 12.00 mmol) in THF (40 mL) was added matrine (1.50 g, 6.00 mmol) in one portion at ice bath. The reaction was stirred at 0 °C for 10 min, refluxed for another 10 h, and then quenched with water (30 mL). After evaporation of THF, the aqueous layer was extracted with ethyl acetate (80 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on alkaline alumina to give compound **1** (1.23 g, 88%) as a white solid, mp 60−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86−2.70 (m, 4H), 2.38−2.32 (m, 2H), 2.21−2.14 (m, 1H), 2.04 (t, J = 4.0 Hz, 1H), 1.99−1.85 (m, 5H), 1.80−1.71 (m, 2H), 1.69−1.50 (m, 5H), 1.48−1.24 (m, 5H), 1.03−0.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.4, 58.3, 57.7, 57.4, 56.5, 56.2, 41.8, 35.3, 29.5, 28.3, 26.3, 25.8, 24.8, 21.7, 21.3; HRMS (ESI) calcd. for $[C_{15}H_{26}N_2+H]^+$ 235.2169, found 235.2173.

*Synthetic Procedure for 1,16-Dioxy-15-deoxymatrine hydrate (**2**).* To a solution of compound **1** (0.78 g, 3.30 mmol) in hydrogen peroxide (30%, 40 mL) was added solid sodium hydroxide slowly at 50 °C. After 30 min, a small amount of manganese dioxide was added to decompose the residual hydrogen peroxide. When cooled and filtered, the filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (DCM: MeOH = 5:1) followed by recrystallization from petroleum ether/acetone to give compound **2** (0.65 g, 68%) as a white solid, mp 196−197 °C (gradually becoming red). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10−4.98 (m, 2H), 4.10 (s, 2H), 3.23−3.00 (m, 8H), 2.79 (dd, J = 8.0, 4.0 Hz, 1H), 2.73−2.42 (m, 4H), 1.93−1.40 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.6, 69.2, 68.7, 68.5, 67.1, 66.3, 34.2, 28.8, 25.1, 24.0, 23.4, 23.0, 20.0, 17.3, 17.2. HRMS (ESI) calcd. for $[C_{15}H_{26}N_2O_2+H]^+$ 267.2067, found 267.2070.

*Synthetic Procedure for 14-R-14-Hydroxymethyl-15-deoxymatrine (**3**) and 14-S-14-Hydroxy methyl-15-deoxymatrine (**4**).* To a solution of i-Pr_2NH (11.3 mL, 80.5 mmol) in THF (10 mL) was added

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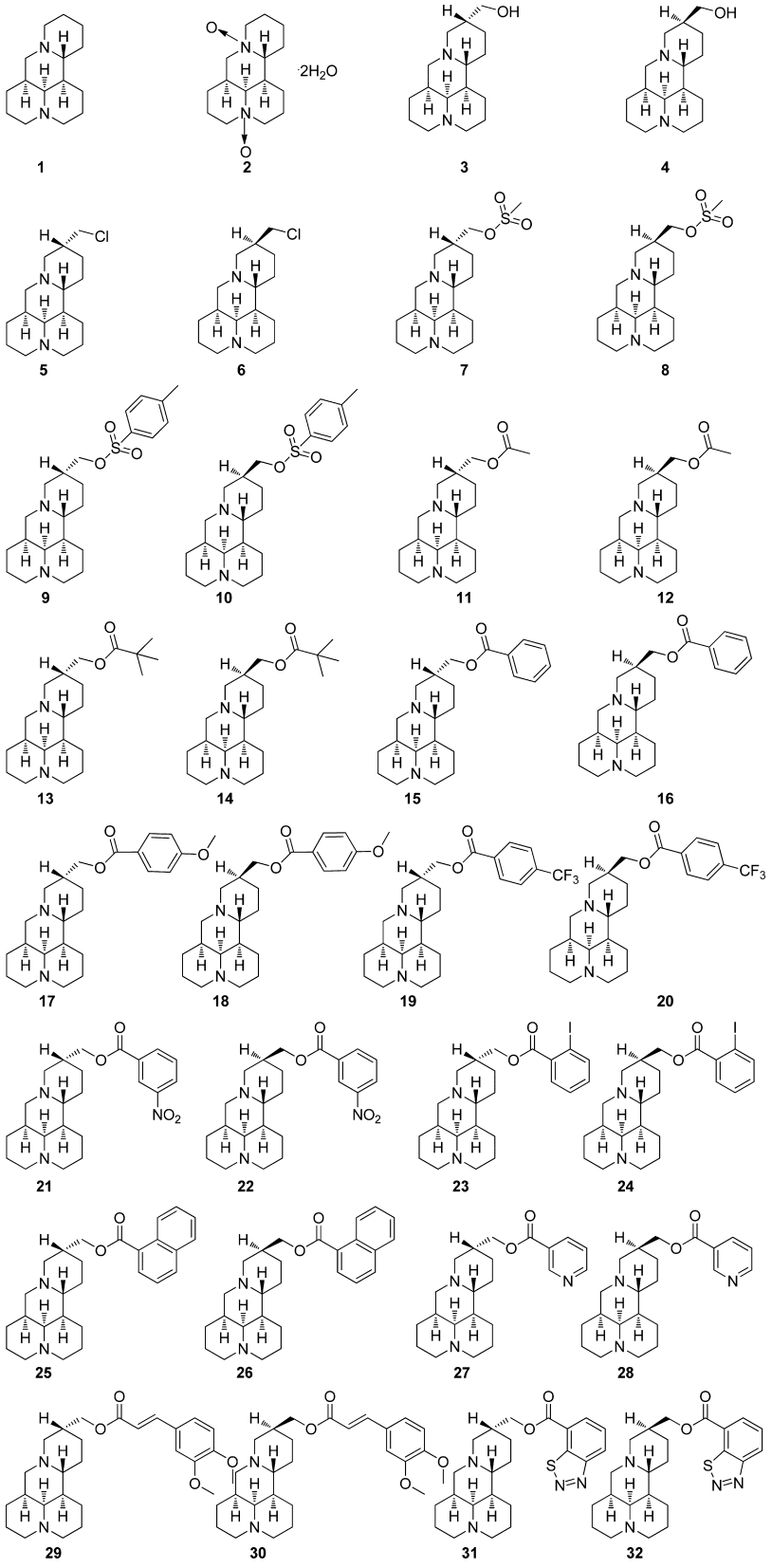

Figure 2. Structures of synthesized matrine derivatives **1**−**32**.

n-BuLi (37.6 mL, 2.4 M in THF, 90.2 mL) dropwise at −78 °C under an atmosphere of argon. After 10 min, a solution of dimethyl carbonate (3.5 mL, 41.9 mmol) in THF (10 mL) was added via a syringe slowly. The reaction mixture was stirred at this temperature for 30 min and then warmed to room temperature naturally. Two hours later, saturated aqueous NH_4Cl (20 mL) was added to quench the reaction. After evaporation of THF, the aqueous layer was extracted with CH_2Cl_2 (80 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give mixture **A** (yield 98%) as yellow oil.

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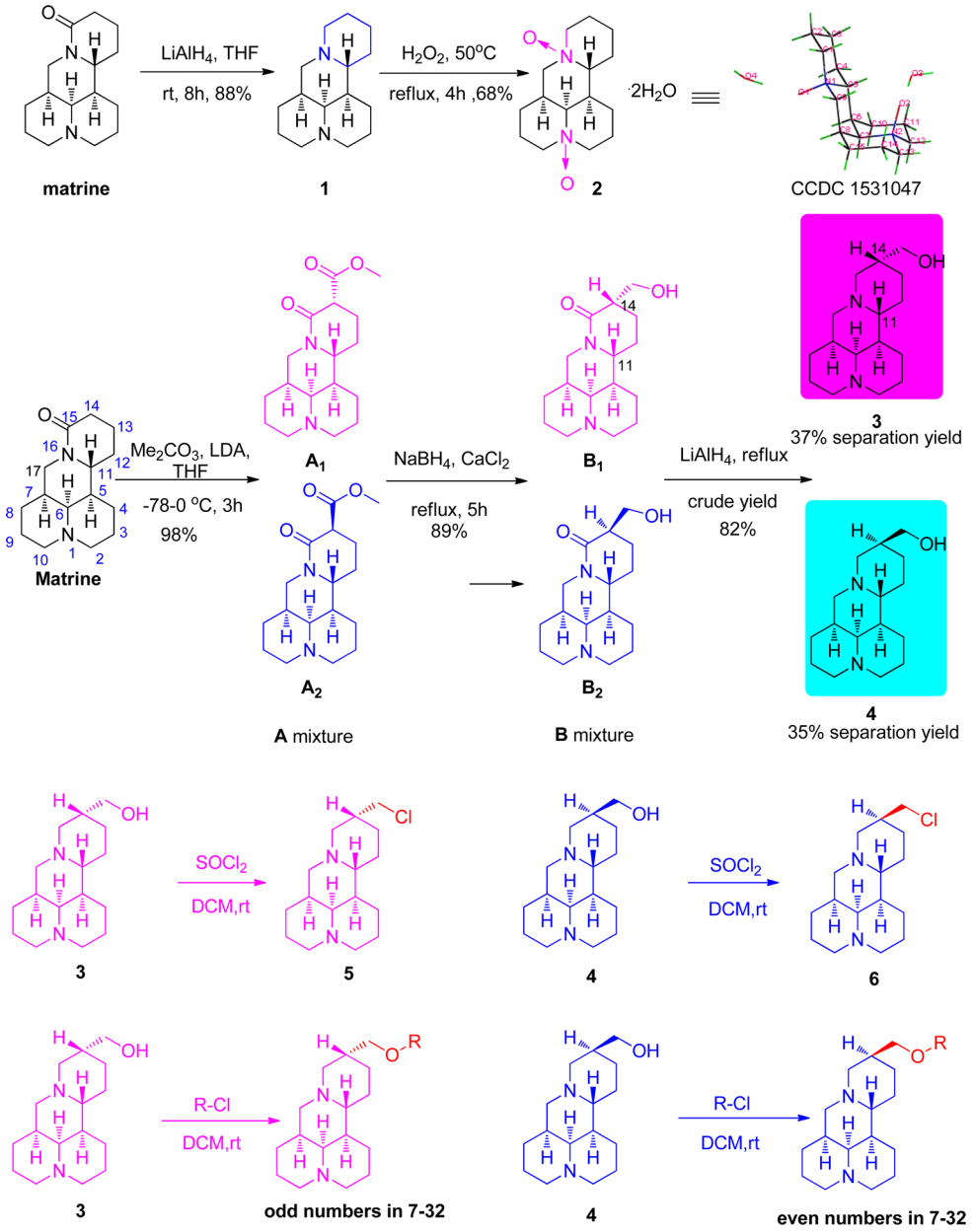

Figure 3. Synthetic routes for **1**−**32**.

To a solution of mixture **A** obtained above in dry methanol (500 mL) was added calcium chloride (10.6 g, 96.6 mmol), then it was added sodium borohydride (7.30 g, 193.2 mmol) in batches at ice bath. When refluxed for 5 h, the mixture was quenched with 20 mL of water. After evaporation of methanol, the aqueous layer was extracted with EA (60 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give white solid **B** (yield 85%).

To a solution of **B** in dry THF (150 mL) was added lithium aluminum hydride (3.60 g, 64.40 mmol) at ice bath, and the mixture was refluxed for 5 h before quenched with water. After evaporation of THF, the aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on alkaline aluminum (methylene chloride with 1% aqueous ammonia/petroleum ether =1:1) to give compounds **3** and **4**.

Compound **3**: light yellow solid (3.1 g, 37%), mp 146−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02−3.98 (m, 1H), 3.81−3.78 (m, 1H), 2.93−2.90 (m, 1H), 2.85−2.76 (m, 2H), 2.66 (t, J = 12.0 Hz, 1H), 2.57−2.53 (m, 1H), 2.49−2.43 (m, 1H), 2.38 (dd, J = 8.0, 4.0 Hz, 1H), 2.02 (t, J = 4.0 Hz, 1H), 1.97−1.61 (m, 13H), 1.56−1.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.9, 64.1, 59.6, 58.0, 57.6, 57.3, 55.9, 41.9, 35.3, 33.6, 28.9, 28.1, 27.1, 26.1, 21.6, 21.3. HRMS (ESI) calcd. for $[C_{16}H_{28}N_2O+H]^+$ 265.2274, found 265.2276.

Compound **4**: yellow solid (3.0 g, 35%), mp 146−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48−3.39 (m, 2H), 3.38 (s, 1H), 2.95 (d, J = 12.0 Hz, 1H), 2.97−2.71 (m, 3H), 2.40−2.32 (m, 2H), 2.04 (s, 1H), 1.97−1.63 (m, 10H), 1.54−1.29 (m, 6H), 1.10−0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.1, 64.2, 59.5, 58.3, 57.6, 57.4, 56.1, 41.4, 39.1, 35.1, 28.9, 28.2, 27.8, 26.5, 21.7, 21.3. HRMS (ESI) calcd. for $[C_{16}H_{28}N_2O+H]^+$ 265.2274, found 265.2278.

*Synthetic Procedure for 14-R-14-Chloromethyl-15-deoxymatrine (**5**).* To a solution of compound **3** (0.52 g, 2.0 mmol) and in CH_2Cl_2 (40 mL) was added thionyl chloride (0.21 g, 3.0 mmol) dropwise at room temperature. After the reaction mixture was refluxed 2 h, it was washed with diluted aqueous Na_2CO_3, water, and brine. After the solution was dried over Na_2SO_4, it was evaporated under reduced pressure, and the resulting residue was purified by column chromatography on alkaline alumina to give compound **5** (0.48 g, 86%) as a

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white solid, mp 108−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84−3.67 (m, 2H), 2.86−2.76 (m, 3H), 2.66 (t, J = 12.0 Hz, 1H), 2.37−2.31 (m, 2H), 2.25 (dd, J = 8.0, 4.1 Hz, 1H), 2.01−1.86 (m, 7H), 1.81−1.48 (m, 6H), 1.44−1.25 (m, 4H), 1.11−1.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.4, 58.5, 57.8, 57.6, 57.4, 56.1, 47.2, 41.5, 36.8, 35.1, 28.3, 26.5, 26.2, 24.8, 21.8, 21.4. HRMS (ESI) calcd. for $[C_{16}H_{27}ClN_2+H]^+$ 283.1936, found 283.1940.

*Synthetic Procedure for 14-S-14-Chloromethyl-15-deoxymatrine (**6**).* Compound **6** was obtained using a synthetic procedure similar to that of compound **5** as a white solid (0.58 g, 71%), mp 57−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43−3.31 (m, 2H), 3.00 (d, J = 8.0 Hz, 1H), 3.01−2.76 (m, 3H), 2.42−2.34 (m, 2H), 2.05−1.89 (m, 9H), 1.78−1.60 (m, 2H), 1.55 (s, 2H), 1.46−1.31 (m, 4H), 1.11−0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.2, 59.8, 57.9, 57.6, 57.3, 56.0, 48.2, 41.6, 38.7, 35.6, 29.1, 29.0, 28.1, 26.5, 21.7, 21.3. HRMS (ESI) calcd. for $[C_{16}H_{27}ClN_2+H]^+$ 283.1936, found 283.1940.

*Synthetic Procedure for 14-R-14-Methylsulfonyloxymethyl-15-deoxymatrine (**7**).* To a solution of compound **3** (0.69 g, 2.6 mmol) and in CH_2Cl_2 (40 mL) was added methylsulfonyl chloride (0.59 g, 5.2 mmol) dropwise at room temperature. After the reaction mixture was stirred at room temperature for about 2.5 h, it was washed with diluted aqueous $NaHCO_3$, water, and brine. After the solution was dried over anhydrous Na_2SO_4, it was evaporated under reduced pressure, and the resulting residue was purified by column chromatography on alkaline alumina to give compound **7** as a white solid (0.94 g, 80%), mp 106−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48−4.35 (m, 2H), 3.02 (s, 3H), 2.84−2.65 (m, 4H), 2.39−2.34 (m, 2H), 2.20 (dd, J = 8.0, 4.0 Hz, 1H), 2.10−2.08 (m, 1H), 2.01 (t, J = 4.0 Hz, 1H), 1.93−1.70 (m, 7H), 1.60−1.49 (m, 3H), 1.45−1.26 (m, 5H), 1.13−1.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.6, 64.2, 58.3, 57.6, 57.4, 56.5, 56.0, 41.5, 36.9, 35.1, 33.4, 28.2, 26.2, 25.1, 24.9, 21.7, 21.3. HRMS (ESI) calcd. for $[C_{17}H_{30}N_2O_3S+H]^+$ 343.2050, found 343.2058.

*Synthetic Procedure for 14-S-14-Methylsulfonyloxymethyl-15-deoxymatrine (**8**).* Compound **8** was obtained by using compound **4** as substrate and adopting a synthetic procedure similar to that of compound **7** as a white solid (0.92 g, 90%), mp 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11−3.98 (m, 2H), 3.01 (s, 3H), 2.94−2.91 (m, 1H), 2.84−2.74 (m, 3H), 2.40−2.34 (m, 2H), 2.05−2.04 (m, 2H), 1.99−1.84 (m, 7H), 1.77−1.62 (m, 2H), 1.56−1.47 (m, 2H), 1.47−1.31 (m, 4H), 1.12−1.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.4, 64.0, 58.5, 57.8, 57.4, 57.2, 55.9, 41.4, 37.2, 36.0, 35.1, 28.6, 28.1, 27.2, 26.3, 21.5, 21.2. HRMS (ESI) calcd. for $[C_{17}H_{30}N_2O_3S+H]^+$ 343.2050, found 343.2054.

Compounds **9**−**32** were prepared similarly by reacting **3** or **4** with corresponding sulfonyl chloride or acyl chloride. The physical data were provided in the Supporting Information.

Biological Assay. Detailed bioassay procedures for the anti-TMV,[22] fungicidal,[23] and insecticidal[24] activities were described in our published literature and can also be found in the Supporting Information. According to statistical requirements, each bioassay was repeated at least three times. The error of the experiments was 5%.

RESULTS AND DISCUSSION

Synthesis. Compound **1** was synthesized by reducing matrine with $LiAlH_4$, and compound **2** was made by oxidation of **1** with hydrogen peroxide (Figure 3). The optically pure substrates **3** and **4** needed a three-step reaction. The first step was to synthesize compound **A** by reacting matrine with dimethyl carbonate in the presence of LDA at −78 °C. Compound **A** was a mixture of two diastereomers, but the two isomers could not be separated by column chromatography because they had almost the same polarity and occurred at the same place on the TLC plate. In the second step, compound **A** reacted with sodium borohydride to afford compound **B**. Similarly, the two diastereomers of **B** could not be separated due to a situation just like compound **A**. At last, compound **B** was treated with $LiAlH_4$ to give the isomers **3** and **4**, which were successfully separated on an alkaline alumina column using methylene chloride with 1% aqueous ammonia and petroleum ether (volume ratio 1:1) as eluent. The crude yield could reach 82% (separation yield of **3** was 37%, that of **4** was 35%), which ensured further diversity derivation. With optically pure substrates **3** and **4** in hand, a series of sulfate, carboxylate, and heterocycle carboxylate was synthesized (Figure 2) by reacting **3** or **4** with corresponding sulfonyl chloride or acyl chlorides (Figure 3); chlorinated matrines **5** and **6** were synthesized by refluxing **3** and **4**, respectively, with thionyl chloride.

Configuration of 3 and 4. The absolute configurations of 14-C of **3** and **4** were difficult to assign through the ^{1}H NMR spectra analysis, so we decided to analyze the configurations of intermediate $\mathbf{B_1}$ and $\mathbf{B_2}$ to deduce the configurations of **3** and **4**. Though $\mathbf{B_1}$ and $\mathbf{B_2}$ could not be separated by column chromatography as we previously described, by repeated recrystallization (ethyl acetate, petroleum ether), they can be obtained as mixtures with ratios about 3:1 (mixture I) and 1:1 (mixture II). By comparing the NOE difference spectrum of mixture II (Figure S1) and ^{1}H NMR spectra of mixture I and mixture II (Figures S2 and S3), we successfully figured out that 11-H (peak b) and 14-H (peak c) of $\mathbf{B_1}$ were at the same side of the pyridinone ring, which indicated a 14-R configuration. Hence, by reducing mixture I and comparing the obtained quantities of the two products, we could assign compound **3** in higher separation yield to be the one reduced from $\mathbf{B_1}$, therefore also bearing a 14-R configuration.

Though we did not obtain the crystal of **3** or **4** or any one of their derivatives at the beginning of our project, we fortunately obtained the single-crystal of compound **2** in its dihydrate form. In fact, X-ray diffraction of compound **2** not only well explained the extra peaks around 4.10 ppm in ^{1}H NMR spectrum, but also clarified the spatial configuration of 1,16-dioxy-15-deoxymatrine (Figure 3 and Figure S4), which could be used to deduce the configuration of compounds **3** and **4**. Since we could know from Figure S4 that the oxygen atom at N1 was at the trans position to the hydrogen at C5 (numbering in the X-ray drawing of **2**), we could deduce that in compounds **3** and **4** the lone pair electrons at N1 are also trans to the hydrogen at C11 (C5 in the X-ray drawing of **2**). Therefore, in compound **3**, the hydroxymethyl group is at the same direction with the lone pair electrons, and they should form intramolecular hydrogen bond (Figure S5); thus, **3** should have less polarity and occur in the upper position on TLC plate. That is truly the case. Fortunately, we finally obtained the single crystal of compound **17** (Figure S6), a derivative of compound **3**, which proved the correctness of configuration assignment of compounds **3** and **4**.

Antiviral Activity. A series of matrine analogues was synthesized and assessed the antivirus activity against tobacco mosaic virus (TMV) in four modes (in vitro, inactivation effect, curative effect, and protection effect in vivo), with commercial ribavirin and NK-007, an efficient antivirus compound created by our group previously, as standards (Table 1). Compared with matrine, compound **1** had increased anti-TMV activity more or less after reducing the amide in matrine to tertiary amine, and when both nitrogen atoms were oxidized, **2** had decreased activity (**1** > matrine > **2**), which indicated that the lone pair electrons of the two nitrogen atoms was beneficial to the activity. The 14-hydroxymethyl-15-deoxymatrine was a pair of diastereoisomers, of which the one in 14-*R* configuration was **3**, and the one in 14-*S* was **4**. The two compounds had remarkable differences: the activity of **3** (67.3%, 69.2%, 63.7%, 63.0% at 500 μg/mL for in vitro activity, inactivation, curative and protection activities in vivo, respectively) was approximately equal to

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Figure 4. Representative pictures of compounds in anti-TMV assay (curative effect, in vivo, at 500 μg/mL) after 3 days.

that of NK-007 (70.3%, 66.1%, 68.4%, 67.5% at 500 μg/mL) (Figure 4), whereas compound **4** was less than matrine (NK-007 > **3** > matrine > **4** ≈ ribavirin). We noticed that **3** could form an intramolecular hydrogen bonding between the hydroxyl hydrogen and tertiary nitrogen, but **4** could not, so we presumed that the hydroxyl of 14−OH in free style may be detrimental to the activity. Therefore, we further synthesized the chlorides and several pairs of esters from **3** and **4**, respectively, to study how this difference could affect their activities.

The result showed that when compounds **3** and **4** were separately converted to chlorides **5** and **6**, the anti-TMV activity of **6** was better than **5**. Similarly, after **3** was converted into esters, the activities of the derivatives decreased obviously, but some of them still had higher anti-TMV activities than matrine such as 14-*R*-methylsulfonate (**7**), 14-*R*-acetate (**11**), 14-*R*-(3-nitro)benzolate (**21**), 14-*R*-(2-iodo)benzolate (**23**), and 14-*R*-*β*-(3,4-dimethoxyphenyl)acrylate (**29**). Comparably, the activities of derivatives from compound **4** increased remarkably; 14-*S*-methylsulfonate (**8**), 14-*S*-acetate (**12**), 14-*S*-pivalate (**14**), 14-*S*-benzolate (**16**), 14-*S*-(3-nitro)benzolate (**22**), 14-*S*-(2-iodo)benzolate (**24**), 14-*S*-naphthoate (**26**), and 14-*S*-*β*-(3,4-dimethoxyphenyl)acrylate (**30**) all exhibited higher activity than matrine, especially the activity of 14-*S*-benzolate (**16**) (66.7%, 60.7%, 63.8%, 68.9% at 500 μg/mL) was close to that of NK-007. It turned out that although the activity of substrate **4** was lower than **3**, the corresponding esters of **4** had similar activities to esters of **3** with the same acid or even higher than that of **3**. However, the substituent effect of these compounds was unobvious.

Since benzo-1,2,3-thiadiazole-containing carboxylic acid was also reported to have considerable anti-TMV activity,[25] we prepared esters **31** and **32** by reacting **3** and **4** separately with benzo-1,2,3-thiadiazole-7-carboxylic acid (**C**) (Table 2) to investigate if the two parts have a synergistic effect. Table 2 showed that the activity of **32** (74.6%, 76.9%, 72.3%, 75.7% at 500 μg/mL) was much higher than **4** (43.5%, 41.2%, 35.9%, 37.3%, 43.5% at 500 μg/mL) and **C** (61.0%, 63.5%, 59.8%, 62.4% at 500 μg/mL), which showed that the existence of the ester group in **32** is beneficial to the activity, and this also meant that the fragments of **4** and **C** in **32** may have a synergistic effect. On the other hand, the activity of **31** was lower than **3** and **C**, which showed the fragments of **3** and **C** in **31** have a negative synergistic effect, and this further demonstrated that the esterification of **3** was detrimental to the anti-TMV activity. We also noticed that **31** (57.9%, 60.0%, 53.0%, 55.8% at 500 μg/mL) had lower activity than **3**+**C** (68.4%, 71.8%, 70.0%, 71.2% at 500 μg/mL), and **32** had higher activity than **4**+**C** (43.4%, 54.1%, 51.9%, 61.2% at 500 μg/mL); this phenomenon suggested that **31** and **32** would not discompose quickly to **3**, **4**, and **C** in plant to exhibit their own activities.

Fungicidal Activity. Generally, matrine and its derivatives all exhibited fungicidal activities to some extent against 14 kinds of

Table 2. In Vitro and in Vivo Antiviral Activities of 31, 32, and related compounds against TMV[a]

compd	conc (μg/mL)	in vitro inhibition rate (%)	in vivo		
			inactivation effect (%)	curative effect (%)	protection effect (%)
 C	500	61.0±1.5	63.5±2.3	59.8±1.0	62.4±1.2
		16.8±1.0	19.6±1.2	14.3±0.5	8.9±0.9
31	500	57.9±1.3	60.0±2.8	53.0±1.6	55.8±1.0
	100	24.3±1.1	19.5±0.8	26.8±1.3	29.4±0.5
3+**C**[a]	500	68.4±2.0	71.8±3.0	70.0±1.9	71.2±1.0
	100	17.6±0.8	27.4±1.0	21.7±0.9	12.9±1.3
32	500	74.6±0.8	76.9±3.3	72.3±2.3	75.7±2.0
	100	31.7±1.0	34.0±1.1	38.8±1.2	32.0±1.0
4+**C**[a]	500	43.4±1.0	54.1±1.2	51.9±1.0	61.2±1.1
	100	35.5±0.9	39.7±1.0	34.1±1.7	29.8±1.0

[a]The molar ratio of the tow components in the mixture is 1:1. The data are presented in means ± SD.

plant pathogens (*Fusarium oxysporum sp. cucumeris*; *Cercospora arachidicola Hori*; *Physalospora piricola*; *Rhizoctonia cerealis*; *Bipolaris maydis*; *Colletotrichum orbiculare*; *Fusarium moniliforme*; *Alternaria solani*; *Fusarium graminearum*; *Phytophthora infestans*; *Phytophthora capsici*; *Sclerotinia sclerotiorum*; *Botrytis cinerea*; *Rhizoctonia solani*) by mycelial growth method (Table 3). The inhibitory rate of many derivatives exceeded 60% at 50 μg/mL. Among these compounds, three compounds, 14-*R*-14-(4-methylsulfonyl)oxymethyl-15-deoxymatrine (**5**), 14-*R*-14-[2-E-3-(3,4-dimethoxyphenyl)acryloyl]oxymethyl-15-deoxymatrine (**29**), and 14-*S*-14-(benzo[*d*][1,2,3]thiadiazole-4-carbonyl)-oxymethyl-15-deoxymatrine (**32**), had more than 70% inhibition rate for *R.C.*, and other three compounds, 14-R-14-hydroxymethyl-15-deoxymatrine (**3**), 14-R-14-(4-methyl) benzenesulfonyloxymethyl-15-deoxymatrine (**9**), and 14-S-14-chloromethyl-15-deoxymatrine (**6**), had more than 70% inhibition rate for *B.C.* Moreover, compound **32** showed higher fungicidal activity against *P.C.* (96.4%, at 50 μg/mL). It showed that these 15-deoxymatrine derivatives had a broad spectrum of fungicidal activity. However, compared with commercial fungicides carbendazim and chlorothalonil, these derivatives were less potent.

Insecticidal Activities. Matrine and its derivatives all exhibited insecticidal activities against five kinds of insect larvae (including *Mythimna Separate*, *Helicoverpa Armigera*, *Ostrinia Nubilalis*, *Plutella xylostella*, and *Culex Pipiens Pallens*), and they showed high selectivity. Many compounds exhibited higher activities than matrine, and most of the derivatives showed very good larvacidal activities against *C. Pipiens Pallens*, especially compounds **4**, **5**, and **22** exhibited obviously higher activities (60%, 60%, 70% at 1 μg/mL). Furthermore, most of matrine derivatives had very good insecticidal activity against *P. xylostella* (half of them had 100% fatality at 600 μg/mL), especially the activities of compounds **13** and **14**, which were 40% and 30%

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Table 3. Fungicidal Activity of Compounds 1−32 against 14 Kinds of Phytopathogens[a]

Compd	Fungicidal activity (%)/50 μg/mL													
	F.C[a]	*C.H*	*P.P*	*R.C*	*B.M*	*C.O*	*F.M*	*A.S*	*F.G*	*P.I*	*P.C*	*S.S*	*B.C*	*R.S*
1	14.7	40.7	67.4	51.7	38.7	30.0	20.0	18.8	10.0	11.8	45.2	62.1	60.0	61.9
2	0.0	33.3	27.9	23.3	35.5	13.3	20.0	31.3	26.7	11.8	35.5	31.8	60.0	67.1
3	8.8	22.2	51.2	28.3	16.1	6.7	10.0	43.8	33.3	11.8	41.9	48.5	70.0	42.9
4	5.9	11.1	27.9	23.3	9.7	6.7	0.0	60.0	23.3	23.5	35.5	31.8	62.0	42.9
5	38.2	37.0	62.8	70.0	6.5	13.3	10.0	31.3	13.3	17.6	38.7	31.8	52.5	19.0
6	52.9	48.1	51.2	60.0	22.6	40.0	20.0	31.3	26.7	11.8	68.1	37.9	70.0	57.1
7	17.6	22.2	41.9	31.7	16.1	13.3	20.0	43.8	43.3	41.2	67.7	48.5	57.5	42.9
8	8.8	18.5	27.9	31.7	3.2	10.0	5.0	18.8	13.3	23.5	48.4	50.0	67.5	57.1
9	8.8	22.2	39.5	23.3	16.1	13.3	15.0	43.8	20.0	17.6	48.4	45.5	77.5	66.7
10	2.9	33.3	39.5	31.7	12.9	13.3	20.0	60.0	26.7	11.8	38.7	27.3	57.5	42.9
11	26.5	22.2	62.8	60.0	16.1	26.7	30.0	43.8	13.3	17.6	48.4	28.8	50.0	47.6
12	8.8	29.6	32.6	31.7	9.7	13.3	20.0	37.5	10.0	17.6	38.7	19.7	12.5	33.3
13	2.9	37.0	34.9	15.0	22.6	30.0	10.0	43.8	13.3	11.8	45.2	30.3	35.0	47.6
14	2.9	22.2	16.3	35.0	41.9	46.7	20.0	62.5	63.3	29.4	64.5	36.4	60.0	52.4
15	47.1	63.0	62.8	53.3	45.2	46.7	20.0	31.3	33.3	23.5	61.3	45.5	65.0	38.1
16	68.8	59.3	62.8	65.0	38.7	43.3	25.0	25.0	33.3	23.5	38.7	30.3	15.0	33.3
19	2.9	18.5	48.8	23.3	6.5	6.7	5.0	18.8	26.7	17.6	38.7	28.8	37.5	38.1
20	0.0	7.4	23.3	30.0	0.0	6.7	5.0	43.8	40.0	41.2	48.4	27.3	35.0	38.1
21	17.6	37.0	32.6	31.7	6.5	6.7	10.0	31.3	33.3	17.6	65.2	12.1	27.5	19.0
22	8.8	33.3	39.5	23.3	16.1	13.3	10.0	37.5	13.3	23.5	48.4	30.3	57.5	47.6
23	8.8	22.2	39.5	23.3	9.7	13.3	5.0	25.0	20.0	17.6	38.7	27.3	20.0	38.1
25	11.8	48.1	16.3	26.7	16.1	16.7	15.0	26.7	36.4	31.3	32.1	39.5	13.9	39.5
25	23.3	34.5	28.6	66.7	18.4	16.1	19.4	26.7	33.3	31.3	14.3	13.2	27.8	6.2
26	25.6	27.6	26.8	34.6	18.4	12.9	16.1	33.3	36.4	37.5	42.9	26.3	13.9	3.7
27	25.6	34.5	35.7	55.6	15.8	0.0	19.4	26.7	36.4	37.5	35.7	26.3	33.3	12.3
28	23.3	55.2	26.8	48.1	23.7	16.1	25.8	33.3	33.3	25.0	42.9	28.9	8.3	18.5
29	0.0	22.2	20.9	73.3	16.1	13.3	20.0	43.8	23.3	41.2	41.9	13.6	17.5	42.9
30	0.0	11.1	27.9	36.7	19.4	13.3	10.0	25.0	23.3	5.9	41.9	15.2	20.0	14.3
31	20.9	34.5	33.9	39.5	18.4	16.1	22.6	33.3	36.4	37.5	53.6	19.7	27.8	24.7
32	27.9	48.3	53.6	76.5	26.3	25.8	35.5	56.3	63.3	76.5	96.4	40.9	40.0	52.4
matrine	14.7	22.2	34.9	55.0	22.6	10.0	15.0	25.0	23.3	5.9	41.9	15.2	20.0	14.3
Carbendazim	<50	<50	<50	100	100	100	<50	<50	100	100	<50	100	<50	100
Chlorothalonil	100	73.3	100	100	91.3	91.3	100	73.3	<50	86.4	100	<50	100	100

[a]*F.C., Fusarium oxysporum* sp. cucumeris; *C.H., Cercospora arachidicola* Hori; *P.P., Physalospora piricola*; *R.C., Rhizoctonia cerealis*; *B.M., Bipolaris maydis*; *C.O., Colletotrichum orbiculare*; *F.M., Fusarium moniliforme*; *A.S., Alternaria solani*; *F.G., Fusarium graminearum*; *P.I., Phytophthora infestans*; *P.C., Phytophthora capsici*; *S.S., Sclerotinia sclerotiorum*; *B.C., Botrytis cinerea*; *R.S., Rhizoctonia solani*.

at 100 μg/mL, but matrine itself had no activity at the same concentration (Table 4). However, though some compounds exhibited high selectivity and good insecticidal activity on some species, the potency of these compounds as insecticide was not comparable with that of commercial insecticides. More modification on the structure should be conducted.

In summary, compared with natural compound matrine, when the amido of matrine was reduced to tertiary amine, most derivatives had significantly increased anti-TMV activity; it can be further illustrated that 15-carbonyl was adverse to the anti-TMV activity. Chirality of 14-carbon could also influence the activities; for most compounds, compounds with 14-S configuration had equivalent to or much better anti-TMV activity than corresponding compounds with 14-R configuration. Among them, compounds **3**, **16**, and **32** exhibited the most potent anti-TMV activity, which could be further

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Table 4. Larvacidal Activities against Oriental Armyworm (*Mythimna Separate*), Cotton Bollworm (*Helicoverpa Armigera*), Corn Borer (*Ostrinia Nubilalis*), Diamond Back Moth (*Plutella xylostella*), and Mosquito (*Culex Pipiens Pallens*) of Compounds 1−32

	larvicidal activity (mortality %) at concn (μg/mL)				
compd	*H. armigera* 600	*O. nubilalis* 600	*M. separata* 600	*P. xylostella* 600/200/100	*C. pipiens pallens* 10/5/2/1
1	15	25	10	0	100/100/100/0
2	45	55	40	0	100/100/100/40
3	15	25	15	0	100/100/40/0
4	35	40	30	0	100/100/100/60
5	55	55	50	100/40/0	100/100/100/60
6	15	40	20	100/30/0	100/100/100/20
7	15	25	10	0	100/100/100/20
8	45	60	5	0	100/100/0/0
9	15	30	30	100/100/20	100/100/40/0
10	20	35	15	100/40/0	100/100/40/0
11	65	70	65	0	100/100/40/0
12	30	45	35	0	100/100/60/0
13	35	35	35	100/85/40	100/100/40/0
14	35	50	35	100/100/30	100/100/40/0
15	20	30	25	100/40/0	100/100/60/0
16	10	25	15	80/0/0	100/100/40/0
19	25	35	25	100/0/0	100/100/60/0
20	15	30	20	90/30/0	100/100/40/0
21	25	40	20	100/0/0	100/20/0/0
22	55	70	50	90/0/0	100/100/100/70
23	0	0	0	30/0/0	100/100/20/0
24	0	0	0	55/0/0	100/100/40/0
25	0	0	0	60/0/0	100/55/0/0
26	20	10	0	100/0/0	100/40/0/0
27	0	0	0	100/75/0	100/65/0/0
28	40	0	20	0	100/40/0/0
29	15	35	15	100/0/0	100/100/60/0
30	15	25	10	100/0/0	100/100/40/0
31	20	40	35	30	100/20/0/0
32	45	45	50	100/40/0	100/100/100/40
matrine	30	40	10	0	100/100/100/0

investigated. In addition, matrine and its derivatives had a broad spectrum fungicidal activity and highly selectivity on the insecticidal activity against *C. Pipiens Pallens* and *P. xylostella*. The reported work was just a beginning for matrine, and further structure expeditions and bioactivity evaluations about matrine derivatives are undergoing and will be reported in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.6b05474.

Figures for determination of configuration of **3** and **4**; physical−chemical data for compounds **9**−**32**; ^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**32**; detailed bioassay methods for anti-TMV, fungicidal, and insecticidal activities (PDF)

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Notes

The authors declare no competing financial interest.

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